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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,703	07/31/2001	Gerald Krystal	50216/003004	6548

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EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/11/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,703	KRYSTAL ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,19 and 20* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 7 July 2003 (Paper No.11) as to amendment of claims 1, 3, 12 and 19-20 and cancellation of claims 11, 13-18 and 21-23, and applicants' request for extension of time of three months (filed 7 July 2003, Paper No. 10) have been entered. Also, the applicants' declaration under C.F.R. 1.132 of Simon W. Rabkin filed 10 July 2002 have been entered and considered.

Claims 1-10, 12 and 19 are pending to which the following is or remains applicable. Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Election/Restriction

The response filed 7 July 2003 asserts that the peptide sequences of SEQ ID NOs: 1-8 should be examined together without imposing an undue burden on the Examiner. The peptide sequences of SEQ ID NOs: 1-8 differ from one another in their structure; e.g., the amino acid sequence SEQ ID NO:1 (elected): SVDVEY is structurally distinct from SEQ ID NO:2 YVDVDT. Therefore, separate searches are required for the sequences, which would result in a serious burden to Examiner.

Also, the response argues against that cell death is not an intrinsic feature of the disease states rather a consequence of the disease. This argument is found unpersuasive because cell death is a common event for both disease state and non-disease state: e.g., blood red cells have a biological turnover time of 120 days.

Thus, the requirement is still deemed proper and is therefore made FINAL.

IDS

The response filed 7 July 2003 states that applicants has submitted the Form PTO-1449 and IDS documents and requests that the Form be considered and returned (se page 15). Examiner, however, cannot find the said IDS and the Form PTO-1449 thereof in the current application; thus, the information referred to therein has not been considered as to the merits. Applicants are welcome to provide the IDS references. Applicants are advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C (1).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of <u>preventing</u> cell death in a warm-blood animal comprising administering the same. Applicant is in possession of treating cell death in a warm-blood animal

comprising administering the peptide of SEQ ID NO:1 or a polypeptide comprising Val-Asp-Val (VDV) core sequence(s).

The current invention is directed to prevent cell death comprising administering to the subject the above-mentioned composition, wherein the subject suffers from cardiovascular disease. The specification has set forth the working examples with respect to amelioration of cell death by synthesized streptokinase peptide fragments in cultured cardiac myocytes (examples 1 and 3), in human hematopoietic cell line (examples 5 and 6), and in isolated intact rat heart (example 4). However, the specification provide insufficient guidance and teaching regarding prevention of cell death in cardiovascular tissues or/and organs using the VDV containing peptide in a mammal.

Cell death in an animal is an irreversible biological event which cannot be completely avoided, i.e., prevented. The current application provides no guidance and working examples as to how cell death can be completely avoided, i.e., prevented. Further, the specification fails to describe how to prevent cell death comprising use of the peptide set forth in the instant claims and additional representative example in this regard. Thus, Applicant was not in possession of method of preventing cell growth in a warm-blooded animal comprising administering to said animal the peptide as claimed. *See University of California v. Eli Lilly and co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Also, claims 1-10, 12 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for amelioration or treatment cell death in cultured cardiac myocytes by administering to the subject cells streptokinase (see Example 1 and Table 1), does not reasonably provide enablement for a method of treating or preventing cell death in warm-blood animal (i.e., a mammal) comprising administering to the subject the peptide comprising VDV sequence (note that the peptide degradation during administering process and biological half-life of the peptide is unpredictable). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breath of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/The nature of the invention:

Claim 1 of the current application sets forth a method of treating or preventing cell death in a warm-blood animal comprising disserting to the animal the claimed peptides having the core sequence VDV (Val-Asp-Val).

At issue herein is whether or not the claimed method would function "for preventing cell death in a mammal (warm-blood animal), which is associated with cardiovascular disease (see claim 19). The nature of the invention is the administration of the synthesized peptide containing the core sequence that prevents a mammalian subject from cell death in cardiovascular system and prevent the subject from having cardiovascular disease thereof. The specification has set forth working examples with respect to amelioration of cell death by synthesized streptokinase peptide fragments thereof in cultured cardiac myocytes (examples 1 and 3), in human hematopoietic cell line (examples 5 and 6), and in isolated intact rat heart (example 4). Yet, the specification does not provide working example and guidance as to preventing cell death in cardiovascular tissues or/and organs. Thus, the claim language "preventing cell death" would render the claims so broad that the scope of claims is outside the bounds of the enablement and would have resulted in the necessity of undue experimentation.

Since cell death in an animal is biologically irreversible, unavoidable, thus unpreventable, and since the specification provides no working examples as to how cell death can be completely avoided, *i.e.*, prevented, undue experimentation is required to practice the claimed invention. The application needs to provide sufficient written description regarding this in order for enablement.

On the other aspect, the specification provides insufficient guidance and no working examples as to the issue of peptide degradation in vivo. The N-end rule indicates that the peptide

with bulky amino acid residue (e.g., tyrosine) at N-terminus has extremely short half-life in vivo (see Varshavsky, A. (1996) *Proc. Natl. Acad. Sci.* 93, 12142-12149). Thus, amount of the peptide for treating cell death in patient having cardiovascular disease without apparent cytotoxicity is highly unpredictable.

Since cellular model study has not correlated well with in vivo clinical trial results in patients for treating cardiovascular disease. Since the method of prophylaxis indices of administering to the animal the peptide can be species- and model-dependent, it is not clear that reliance on the cellular studies accurately reflects the relative human efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively prophylaxis of cell death in a mammal or reach any therapeutic endpoint in humans by administering considering the peptide biological half-life of the peptide. The specification does not teach how to extrapolate data obtained from cellular studies to the development of effective in vivo mammalian including human therapeutic prevention, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the peptide mediated prevention of cell death thereof in the specification.

(2) The amount of direction or guidance presented:

The specification does not disclose one reasonable method for preventing cell death in a mammal who is suffering from cardiovascular disease, which bears a reasonable correlation to the entire scope of the claims. The specification lacks guidance/direction as to how the claimed peptides, e.g., VDV core sequence containing polypeptide, prevent cell death; thus, how to render the patient survival. The specification needs to provide what is missing in this regard so as to enable the claimed method thereof.

(3) The unpredictability of the art:

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The specification sets forth amelioration of cell death in human cultured cell lines by Trypan blue assay for assessing viability (see example 6, pages 27-28). Yet, the specification is silent in how to extrapolate the result obtained from culture cell study into whole animal (mammal) treatment for cardiovascular disease. The specification provide no working model in this regard.

Thus, clinical trial results in patients as to preventing cell death is necessary for enabling. As stated above, the peptide being administered for treating or preventing cell death is confronted with peptide degradation which is highly unpredictable in view of half-life of the peptide during the administration thereof. Therefore, it is unclear that the skilled artisan could predict the consequence of treating a cardiovascular disease by preventing cell death is highly variable.

Further, results obtained under controlled conditions often differ from the clinical response obtained in patients. There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability of the peptide for preventing cell death in the patient suffering from cardiovascular disease. Applicant's experimental results have relied on culture cells or isolated organ of animal. It is not clear that such model would reflect the therapeutic prevention of cell death in the patient having cardiovascular disease. (see claims 12 and 19).

Thus, the invention is unpredictable in the absence of factual indicia to the contrary.

(4) The quantity of experimentation necessary:

In the absence of working examples with regard to treating or preventing cell death using the synthetic peptide comprising VDV sequence(s), unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and error to practice the claimed invention as to preventing cell death. The quantity of experimentation would be large and unpredictable. One skilled in the art would be required to carry out an undue experimentation for testing for ability of the peptide to prevent cell death in the studied subject.

(5) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of the peptides or analogs thereof. In view of the preceding factors (1-4), the level of skill in this art is high and requires at least a cell biologist or a physician with several years of experience in molecular biology as well as knowledge in cardiology and pharmacology; yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. An unduly level of skill is needed for the skilled artisan to treat cell death in a mammal having a cardiovascular disease by a mean, *e.g.*, preventing cell death thereof.

In consideration of each of factors stated above, absent factual data to the contrary, the amount and level of experimentation needed is undue to practice the claimed method in regard to preventing cell death.

The response to the rejection under 35 USC 112, the first paragraph

The response filed 7 July 2003 argues against the rejection based on the declaration of Simon Rabkin (Paper No. 6) and asserts that Rabkin et al. demonstrate the ability of VDV-containing peptide to ameliorate cell death in animal model for human disease (see the paragraphs on the bridging pages 14-15). The applicants' argument is not persuasive because the declaration does not address the issue regarding how to prevent cell death in a mammal having a disease state, e.g., cardiovascular disease. Note that the cellular data of amelioration cannot substitute for clinical indicia for cell-death prevention in a whole animal (patient) or and cannot extrapolate the result obtained from cell culture into a mammal with regard to effective treatment or effective prophylaxis of cell death in the subject.

Claim Rejections - 35 USC §102 and §103

The reactions are withdrawn in view of the applicants' amendment filed 7 July 2003.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on

the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Samuel W. Liu, Ph. D.

August 4, 2003